UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/735,608	12/12/2003	Marcel P. Bruchez	5100-0702.20	1956

20855 7590 07/11/2006

ROBINS & PASTERNAK
1731 EMBARCADERO ROAD
SUITE 230
PALO ALTO, CA 94303

EXAMINER	
DO, PENSEE T	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 07/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/735,608	BRUCHEZ ET AL.	
	Examiner	Art Unit	
	Pensee T. Do	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 3-41* is/are pending in the application.

4a) Of the above claim(s) *17-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-16 and 38-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1, 3-41* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 16, 2006 has been entered.

Response to Amendment

The declaration under 37 CFR 1.132 filed on June 16, 2006 is insufficient to overcome the rejection of claims 1, 3-16, 38-41 based upon the rejections as set forth in the last Office action because of reasons set forth below in the "response to argument" section.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-7, 10-13, 16, 38, 39, 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bawendi et al. (US 6,306,610) in view of Rothbard et al. (US 6,306,993).

Bawendi teaches a composition comprising fluorescent semiconductor nanocrystals associated to a molecule such as cells, prokaryotic or eukaryotic. The semiconductor nanocrystals comprise a CdSe core and a ZnS shell. The composition is also associated with cell membranes. (see col. 3, line 60-col. 4, line 62; col. 19, lines 58-60; col. 20, lines 51-59; col. 29, lines 41-42).

However, Bawendi fails to teach the nanoparticle is associated with a cationic polymer capable of enhancing the transport of the semiconductor nanoparticle across a biological membrane; wherein the cationic polymer has from 5 to 25 contiguous Lys and/or Arg residues. Bawendi also fails to teach a kit comprising a semiconductor nanoparticle complex according to claims 1, 12, 16 and instructions for preparing the encoded cells using the semiconductor nanoparticle complex. Bawendi also fails to teach the cationic polymer is a tat peptide from protein transduction domain of the HIV tat protein.

Rothbard teaches methods and composition for transporting drugs and macromolecules across biological membranes wherein the biological membranes are contacted with a conjugate containing a biologically active agent that is covalently attached to a transport polymer. Such transport polymer has 6 to 25 subunits of L-Arginine. The transport enhancing polymers are exemplified by peptides in which arginine residues constitute the subunits. Exemplary eukaryotic cell membranes of interest include membranes of dendritic cells, epithelial cells, endothelial cells, keratinocytes, muscle cells, fungal cells, bacterial cells, plant cells and the like. Biological active agents are macromolecules such as nucleic acids, peptides, proteins

and analogs thereof. The agent may be linked to the polymer by a linking moiety. The composition includes a conjugate containing a biological active agent covalently attached to at least one transport polymer and can be packaged with instructions for using it. (see col. 2, line 44-col. 4, line 45; col. 5, lines 47-58). The transport polymers contain short-length polymers from 6 to 25 subunits. The conjugate is effective to enhance the transport rate of the conjugate across the biological membrane relative to the transport rate of the non-conjugate biological agent alone. (see col. 6, line 63-col. 7, line 5). Detecting uptake of macromolecules may be facilitated by attaching a fluorescent tag. (see col. 11, lines 3-4). Fluorescently labeled peptide polymers composed of 6 or more arginine residues entered cells more efficiently than the tat sequence 49-57 in fig. 1 (see col. 11, lines 30-40). Since the polymer of Rothbard composes of 6 to 25 contiguous Arg residues, it must be a cationic polymer.

Since Bawendi and Rothbard both teach using a label such as nanocrystals for cells or cell membrane, it would have been obvious to one of ordinary skills in the art to associate the polymer, which comprises of 6 to 25 subunits of Arg residue, taught by Rothbard to the nanocrystals as a fluorescent label and use in the composition of Bawendi because macromolecules such as peptides and oligonucleotides experience difficulty in passing across the biological membrane and having a polymer as that of Rothbard enhances trans-membrane transport. Furthermore, the nanocrystals of Bawendi can be used a label which associates with the polymer to so that measures of biological molecules transported across the biological membrane can be easily detected because the nanocrystals of Bawendi associates with the biological membrane.

Regarding claims 38, 39 and 41, it would have been obvious to one of ordinary skills in the art to package the combined composition taught by Bawendi and Rothbard with instruction for using it for economical convenience since Rothbard teaches packaging the polymer with biological active agent into a kit with instructions for using it.

Claims 8, 9, 14, 15 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bawendi et al. (US 6,306,610) in view of Frankel et al. (US 5,652, 152).

Bawendi has been discussed above.

However, Bawendi fails to teach that the cationic polymer is tat peptide from the protein transduction domain of the HIV tat protein and a kit comprising the composition of claim 14 with instruction of using. Bawendi also fails to teach the sequence ID NO. 1 comprising of Arg Lys Lys Arg Arg Gln Arg Arg Arg.

Frankel teaches intracellular delivery of cargo molecules by the use of transport polypeptides which comprise HIV tat protein or one or more portions thereof and which are covalently attached to the cargo molecules. The transport polypeptides are characterized by the presence of the tat basic region (amino acids 49-57). The biological active cargo molecules such as polypeptides, nucleic acids are delivered/transported into the cytoplasm and nuclei of cells in vitro and in vivo. (see abstract). Label such as a fluorescent was used to study the transported molecules across the cell membrane. The label is attached to the tat peptide. (see col. 42, lines 24-29). Frankel teaches sequence ID No. 4, amino acids 12-20, comprising Arg Lys Lys Arg Arg Gln Arg Arg Arg. (see col. 55-56, sequence ID. NO. 4).

It would have been obvious to one of ordinary skills in the art to use the HIV tat peptide for transporting biological molecules across the cell membrane as taught by Frankel and attach it to a fluorescence semiconductor nanocrystal which associates to a cell membrane so that when biological molecules to be transported reach the cell membrane, they can be transported effectively and efficiently with the aid of the tat peptide and their activity or measurement can be detected by the nanocrystals since the nanocrystals have a spectral emission that is tunable to a desired wavelength, and wherein said wavelength provides information about a biological state or event. It would have been obvious to one of ordinary skills in the art to package the combined composition into a kit with instruction of using it for economic convenience since Frankel teaches that the tat polypeptide can be used as research laboratory reagents, either alone or as part of a transport polypeptide conjugation kit. (see col. 7, lines 30-32).

Response to Arguments

Applicant's arguments filed June 16, 2006 have been fully considered but they are not persuasive.

The declaration filed on June 16, 2006 states that the nanocrystals are rigid which give less pliant surface for accommodation of the polymers and subsequent transport across the biological membrane, as compared to proteins in the reference taught by Rothbard. Nanocrystals are hydrophobic and are difficult to adhere to non-polar surfaces, such as membranes, through hydrophobic interactions.

The declaration is nothing but an admission that the present invention is not enable. The present invention uses the same polymer and the nanocrystals for

transporting proteins or biomolecules across the cell membrane. However, Dr. Treadway declares that the nanocrystals attached to a transport polymer would not cross the cell membrane. This is also irrelevant to the present invention because the invention claims nothing more than a semiconductor nanoparticle complex comprising of a semiconductor nanocrystal bound to a cationic polymer, regardless of the purpose of which such combination is used for. Bawendi teaches nanocrystals which can be used to visualize location in a cell (see col. 22, lines 30-34). Such teaching translates that nanocrystals must be transported across the cell membrane in order to visualize locations in a cell. Bawendi also teaches that the nanocrystals are coated with a binding pair member such as proteins, receptors, immunoglobulins, etc. to provide a nanocrystal conjugate (see col. 6, line 51-col. 7, line 16). The nanocrystal conjugate is bound to a target. Such target is within the cell (see col. 22, lines 33-34). Thus, Bawendi implies that the nanocrystal conjugate can be transported across the cell membrane to bind with a target within the cell. Rothbard teaches a transport polymer coupled to proteins or biomolecules to be transported across the cell membrane. Such biomolecules coupled to the polymer can be labeled with fluorescent before being transported. (see col. 11, lines 30-40). The transport polymer enhances the transport of biomolecules across the cell membrane. Thus, one of ordinary skills in the art would be motivated to couple nanoparticles with a transport polymer to transport biomolecules across the cell membrane because the transport polymer enhances the transportation.

Applicants further argue that Rothbard states that "the present invention conjugates do not contain large hydrophobic moieties.." and that the nanocrystals of the present invention contain hydrophobic moieties.

However, "large" is the key word in Rothbard's statement. Nanocrystals may contain hydrophobic moieties, but not LARGE hydrophobic moieties.

Applicants also argue that "Rothbard does not teach how to functionalize any and all macromolecules for transport across biological membranes". Only after the experiments performed by the Applicants did it become evident that cationic polymers can in fact facilitate cross-membrane transport of semiconductor nanocrystals.

Rothbard does not need to teach how to functionalize any and all macromolecules for transport across biological membranes because it is irrelevant to the present invention. The present invention is not drawn to a method of making.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Regarding the rejection by Bawendi in view of Frankel, Applicants argue that similar to Rothbard, the "cargo" molecules in Frankel are also biological molecules (peptides, nucleic acid, oligosaccharides. They inherently possess properties suited for biological systems, including hydrophilicity, flexibility, facile conjugation and limited ionic charges (as compared with nanocrystals). Applicants argue that PKAI, the small cargo

molecule used in Frankel, does not have a convenient site for tat conjugation (such as lysine or cysteine residue), and has shown some solubility/precipitation issues. Applicants point out that Frankel does not show that the small cargo molecule "PKAI" to be effectively transported across the biological membrane.

Applicants' argument is not on point. As long as Frankel shows that other molecules to be effectively transported across the membrane, Frankel's invention is valid or that the transport polymer in Frankel is valid. Frankel does not have to show that PKAI is effectively transported because the present invention does not require so. PKAI might not have a "convenient" site for tat conjugation, but other molecules do and the present invention is not drawn to PKAI.

Rothbard and Bawendi teach using labels such as fluorescent labels to detect activity within a cell. Bawendi teaches that the fluorescent semiconductor nanocrystals can be used to visualize location in a cell. (see col. 22, lines 30-34). Rothbard teaches that the fluorescently labeled peptide polymers or the transport peptide linked polymer is used to assess cellular uptake of biological molecules being transported across the cell membrane. (see col. 11, lines 3-33). Frankel also teaches using fluorescent label to study the transported molecules. The label is attached to the tat peptide. (see col. 42, lines 24-29). Thus, one of ordinary skills in the art would have been motivated to combine these references based on those teachings above of Bawendi and Rothbard, or Bawendi and Frankel. Fluorescent tags can be used to assess the cellular uptake of biomolecules and nanocrystals in Bawendi is a fluorescent label. Thus, one of ordinary skills in the art would have reasonable expectation of success when linking the

fluorescent nanocrystal of Bawendi to a transport peptide of Rothbard or Frankel. Applicants argue that "There is absolutely no reason to believe that the carrier peptides employed to transport organic molecules across biological membranes would also successfully transport inorganic nanocrystals across biological membrane". Rothbard and Frankel teach the same transport polymer as the claimed invention, and that such polymer can be linked to a fluorescent tag. Bawendi teaches the same fluorescent semiconductor nanocrystal as the claimed invention and it is a fluorescent tag. Thus, one of ordinary skills in the art would have success in combining these references. If Applicants argue that the transport polymer of Rothbard and Frankel cannot transport inorganic nanocrystal across a biological membrane, then it is no difference that Applicants are admitting that the present invention is not enable. Although, the fluorescent tags of Rothbard and Frankel do not have physical resemblance to the semiconductor nanocrystal, the fluorescent tags of Rothbard and Frankel can emit fluorescent such as the fluorescent nanocrystal of Bawendi. One of ordinary skills in the art would use the either the conventional fluorescent tag or the nanocrystal of Bawendi in order to compare which label gives a more efficient signal through experimentation routine.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pensee T. Do whose telephone number is 571-272-0819. The examiner can normally be reached on Monday-Friday, 7:00-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Pensee T. Do
Patent Examiner
June 29, 2006

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
06/30/06